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Combined Angioma and Glioma (Angioglioma)

VIRA KASANTIKUL, MD, SAMRUAY SHUANGSHOTI, MD,
VIRATT PANICHABHONGSE, MD, AND MARTIN G. NETSKY, MD
From the Department of Pathology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand (V.K., S.S.); Department of Surgery, Bangkok General Hospital, Bangkok, Thailand (V.P.); Department of Pathology, Vanderbilt University School of Medicine, Nashville, Tennessee (M.G.N.)

Ten patients in whom tissue proliferation akin to angioglioma occurred within the brain are described; seven of the lesions were supratentorial and three infratentorial. Only 31 accepted instances of such neoplasms have been found in the literature. The combined lesions usually become symptomatic in the second and third decades. In all 10 cases, the angiomatous part of the combined tumors showed characteristic vascular malformation such as severe hyalinization, tortuosity, and some were even calcified. The number of abnormal blood vessels were excessive in all examples. The glial portion consisted of either astrocytoma, oligodendroglioma, or mixtures of these gliomas. Dedifferentiation of the neuroglia combined with neoplastic endothelial proliferation indicates the true neoplastic nature rather than reactive gliosis associated with a vascular anomaly.

KEY WORDS: angioglioma, brain tumors, angioma, glioma

INTRODUCTION

The term "combined angioma and glioma" or "angioglioma" here means two types of neoplasm (a vascular tumor and a glioma) intermingled in the same mass. Gliomas are by far the most frequent intracranial neoplasms constituting approximately half of all cases of brain tumors [1]. Angiomas comprise about 2% of intracranial lesions but have been reported as high as 7.8% in a series described by Courville [2] in the United States. Angiomas may be found in combination with other tumors in the neuraxis and various neoplastic mixtures have been described in recent years (viz) angiomas with astrocytoma [1,3–5], colloid cysts [6], meningioma [7], and neurilemmoma [8]. The angiomatous proliferation in certain gliomas is often passed off as vascular proliferation and is rarely considered to constitute a distinct and separate neoplastic change [9]. It has been accepted as an entity by Henschen [10] but has been questioned by others [1] and only briefly cited in the extensive review of brain tumors by Zülch [11]. Here, we present 10 cases in which we suggest the diagnosis of angioglioma to be appropriate.

MATERIALS AND METHODS

Tissues in all cases had been fixed in 10% formalin and stained routinely with hematoxylin and eosin (H&E). File slides were used and where appropriate phosphotungstic acid hematoxylin (PTAH), Masson's trichrome, Wilder's reticulin impregnation, and Holzer's preparations were done on the same blocks.

RESULTS

The clinical features and pathologic diagnoses in the 10 pertinent cases are given in Table I. The age of these patients ranged from 5 to 60 years; the median was 33 years; six were men and four were women. Seven neoplasms were supratentorial and three infratentorial. The shortest duration of symptoms was 6 weeks; the longest history extended to 10 years. Infratentorial tumors were associated with a shorter duration of illness. All cases

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Address reprint requests to Vira Kasantikul, M.D., Department of Pathology, Chulalongkorn Hospital, Bangkok 10330, Thailand.

TABLE I. Clinical and Pathologic Features in 10 Cases of Angioglioma

Case no.	Age (yr)	Sex[a]	Location[b]	Duration	Type of glioma	Type of angioma	Outcome
1	5	M	L. Temporoparietal	3 mo	Astrocytoma	Arteriovenous, capillaries	Alive, 3 yr
2	15	F	R. Parietal	2 yr	Astrocytoma	Capillaries, cavernous	Alive, 2 yr
3	31	M	R. Temporoparietal	10 yr	Mixed oligodendroglioma, astrocytoma	Arteriovenous, capillaries	Lost to follow-up
4	35	M	R. Parietal	3 mo	Astrocytoma	Cavernous, capillaries	Alive, 1 yr
5	41	F	R. Frontal	2 yr	Oligodendroglioma	Cavernous, capillaries	Alive, 4 yr
6	58	M	R. Temporal	5.5 yr	Astrocytoma, poorly-differentiated	Vessels, Hyalinized	Died, 1 yr
7	60	F	R. Frontal	1.5 mo	Astrocytoma, poorly-differentiated	Arteriovenous	Died, 5 mo
8	15	M	Cerebellum	1.5 mo	Astrocytoma	Cavernous, capillaries	Alive, 5 yr
9	22	M	Cerebellum	1.5 mo	Mixed oligodendroglioma, astrocytoma	Arteriovenous	Alive, 4 yr
10	57	F	Cerebellum	1.5 yr	Mixed oligodendroglioma, astrocytoma	Arteriovenous capillaries	Alive, 2 yr

[a]M = male; F = female.
[b]L = left; R = right.

had clinical evidence of increased intracranial pressure, including headache, vomiting, and papilledema.

Most patients received radiotherapy after craniotomy and were doing well postoperatively for periods that extended from 9 months to 5 years. Two died within 5 months and 1 year (Cases 6, 7). At necropsy, residual neoplasm was found in Case 7, but postmortem examination was not done in Case 6. The remaining cases had residual symptoms related to the lesion or surgery.

Most of the surgically resected tissue samples ranged in size from 2 cm to 4 cm. Five were largely solid with a homogeneous gray cut surface containing zones of hemorrhage and necrosis; one was cystic.

Microscopically, the neoplastic glial cells in six cases were characterized by widely dispersed fibrillary astrocytes, although some were of the protoplasmic type. The nuclei were irregular and hyperchromatic. Anaplastic cytologic features were seen in two cases (Cases 6, 7) both of which died within 1 year. Three tumors contained both astrocytoma as well as oligodendroglioma. The lesion in Case 5 was oligodendroglioma. Focal hemorrhage and fibrosis were frequent within the tissues. Granules of hemosiderin were scattered throughout the lesions.

The vascular components in these gliomas ranged from capillary endothelial "buds" to cavernous spaces (Figs. 1–3). Case 4 was an astrocytoma in the center of which were many enormous vascular spaces with bridging channels (Fig. 3). These large spaces superficially resembled cysts, but close examination revealed endothelial lining. Connective and glial tissue bridges themselves had additional thin-walled proliferated capillaries as well as convoluted "glomerular" structures. The tissue from Case 5 revealed striking zones of small and large vascular spaces as well as areas of broad collagenous tissue associated with many capillaries. The remainder of the tissue was composed of neoplastic oligodendroglia (Fig. 4). Many hyalinized vessels were noted in Case 6 (Fig. 5).

The size of the angiomatous components was also correlated with angiographic findings. The latter information was not available for Cases 3, 5, and 9. Five lesions had microscopic clusters of abnormal vessels, which represented less than one-fourth of the entire slide when viewed at low power (Cases 1, 2, 5, 7, 9). Three were not imaged by angiography. Intense vascularity, which occupied about one- to two-fourths of the slide was noted in four examples (Cases 3, 6, 8, 10). In Case 4, the angiomatous network comprised more than three-fourths of the slide. Four of these neoplasms (Cases 4, 6, 8, 10) were described as "vascular" by angiography.

DISCUSSION

The concept of angioglioma has been debated by various authors [1,10,12]. Russell and Rubinstein [1] have questioned the existence of this neoplasm as a distinct entity. They contended that most angiogliomas are either highly vascular gliomas, usually astrocytomas, oligodendroglioma, or less likely are vascular malformations surrounded by conspicuous hyperplastic gliosis. Without doubt some reported instances of angioglioma are uncertain in nature and some could have been classified as another glioma with marked vascular proliferation [13]. However, Russell and Rubinstein [1] have described cystic cerebellar tumor that was partly hemangioblastoma and partly glioma in a 70-year-old woman. Henschen, [10], in a review of related literature, found several reported examples prior to 1955 that should be seriously regarded as angioglioma, because these neoplasms consisted largely of numerous abnormal blood vessels in combination with mingled bizarre neuroglia in pertinent lesions. Although Zülch [11] did not describe angioglioma

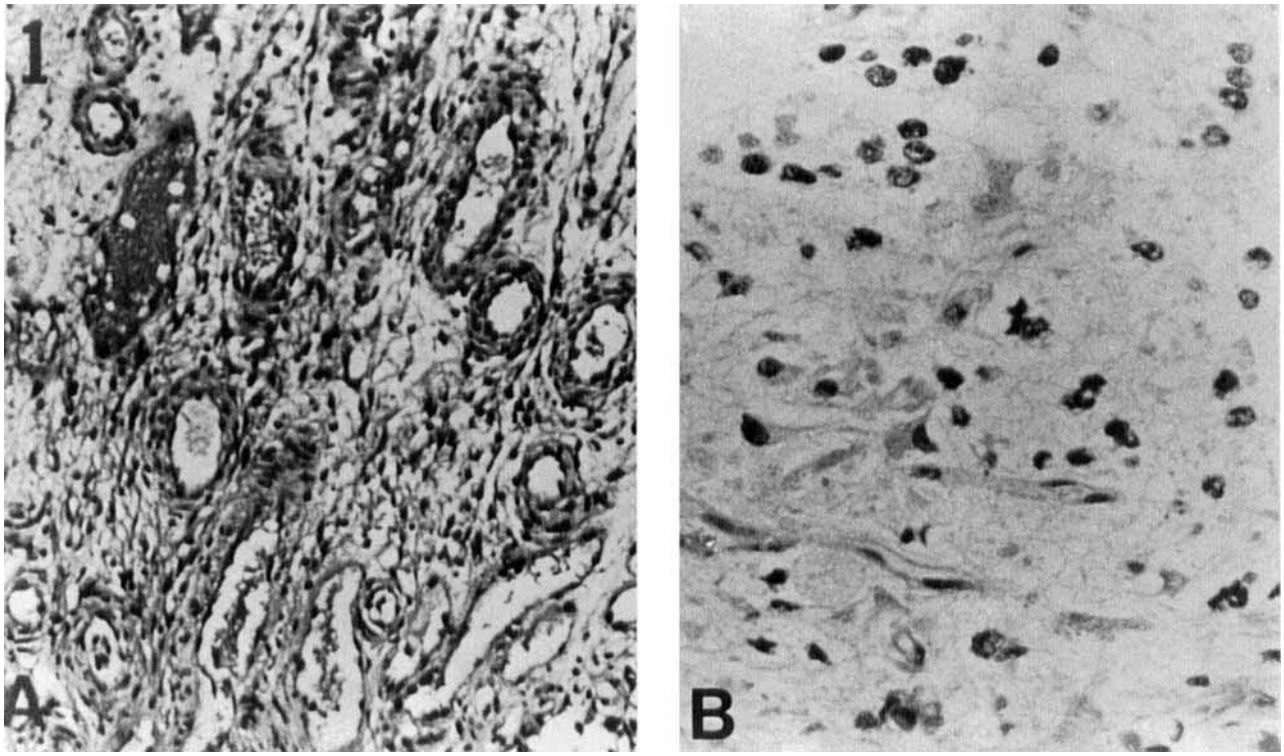

Fig. 1. Photomicrographs in Case 1. **A.** Cluster of arteries, veins, and capillaries (H and E, × 100). **B.** Tumor cells showing darkly staining irregular nuclei and ill-defined cytoplasmic processes (H and E, × 200).

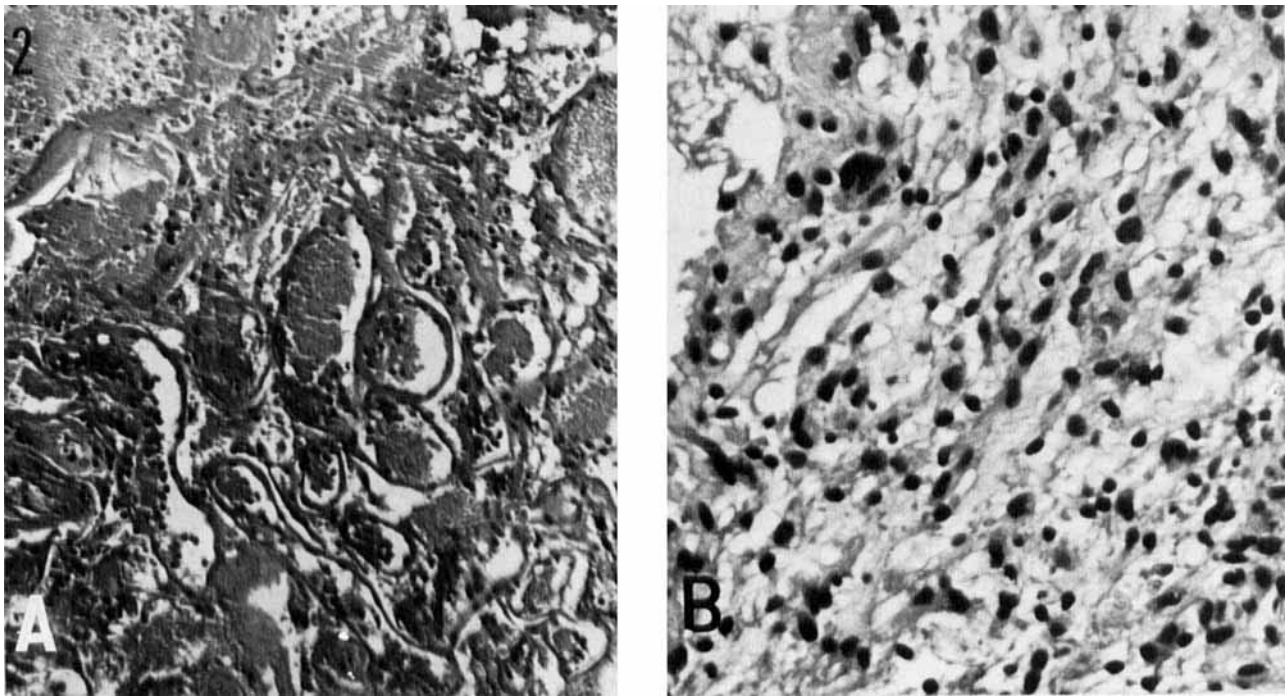

Fig. 2. Angiogliomatous lesion in Case 2. **A.** Numerous thin-walled vessels (H and E, × 100). **B.** Neoplastic astrocytes with pleomorphism (H and E, × 200).

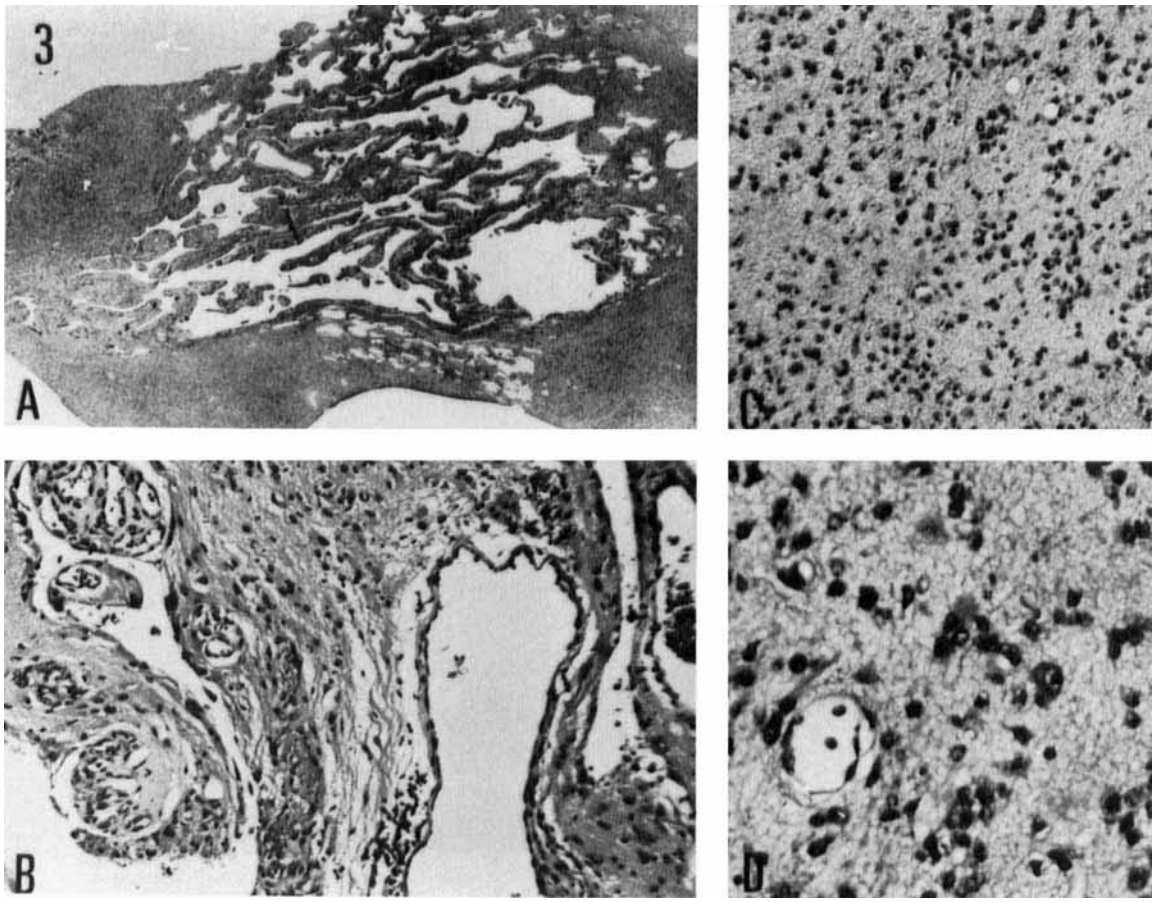

Fig. 3. Cystic angioglioma in Case 4. **A.** Cluster of vascular spaces in the center of glioma resembling "cyst" (H and E, × 25). **B.** Higher power view showing the endothelial cells lining these vascular lumen. Note the "glomerular" structures in the connective and glial tissue bridges (H and E, × 100). **C.** Adjacent astrocytoma (H and E, × 100). **D.** Details of neoplastic cells (H and E, × 200).

in detail, he did point out the vascularity in certain gliomas as being "sometimes clustered together like an angioma." In a review of vasculature of neural neoplasms, Waggener and Beggs [14] commented that a significant number of astrocytomas contained many ectatic atypical vessels resembling a malformation. The neoplasms we have designated as angiogliomas could be diagnosed depending on the sampling as well as the field viewed independently as neoplasms of glial tissue or as hemangioma.

Reluctance to diagnose the dual nature of these lesions arises in part because of acceptance of the origin of cancer from a single cell and application of the laws of parsimony. Increasingly, however, the field theory of the origin of cancer has gained wider acceptance, and multifactorial causation is being recognized. Even one environmental factor such as nitrosamine may cause neoplasms of both glia and connective tissues in the same animal of origin [15].

Angioma is viewed by us as an abnormal localized collection of an excessive number of blood vessels in various stages of differentiation. Such lesions may consist predominantly of arteries, or veins, or capillaries but often may be found combined [16]. They are undoubtedly congenital origins for some of these abnormal proliferations such as those found in the newborn or in combination with other congenital anomalies or found incidentally at necropsy [16,17]. Angioma also may be acquired as in traumatic arteriovenous fistula formation, or indeed could result from reaction of tissue to tumor angiogenesis factor(s) or endothelial growth factor produced by glial neoplasms [8,18]. Regardless of these diverse causes, angioma can be diagnosed morphologically when an abnormal localized collection of blood vessels is sufficient to warrant an independent diagnosis as in the cases herein presented. The malformed nature of these vessels may be recognized as abnormalities in both structure and in number.

Dedifferentiation of neuroglia as characterized by cellular pleomorphism combined with endothelial proliferation in all cases supports the interpretation of their neoplastic nature rather than ascribing them to any form of reactive gliosis. We are aware of the difficulty in many instances in distinguishing between reactive and neoplastic neuroglia. Strong evidence of glioma may be reflected in the number and structural features of the glial cells as

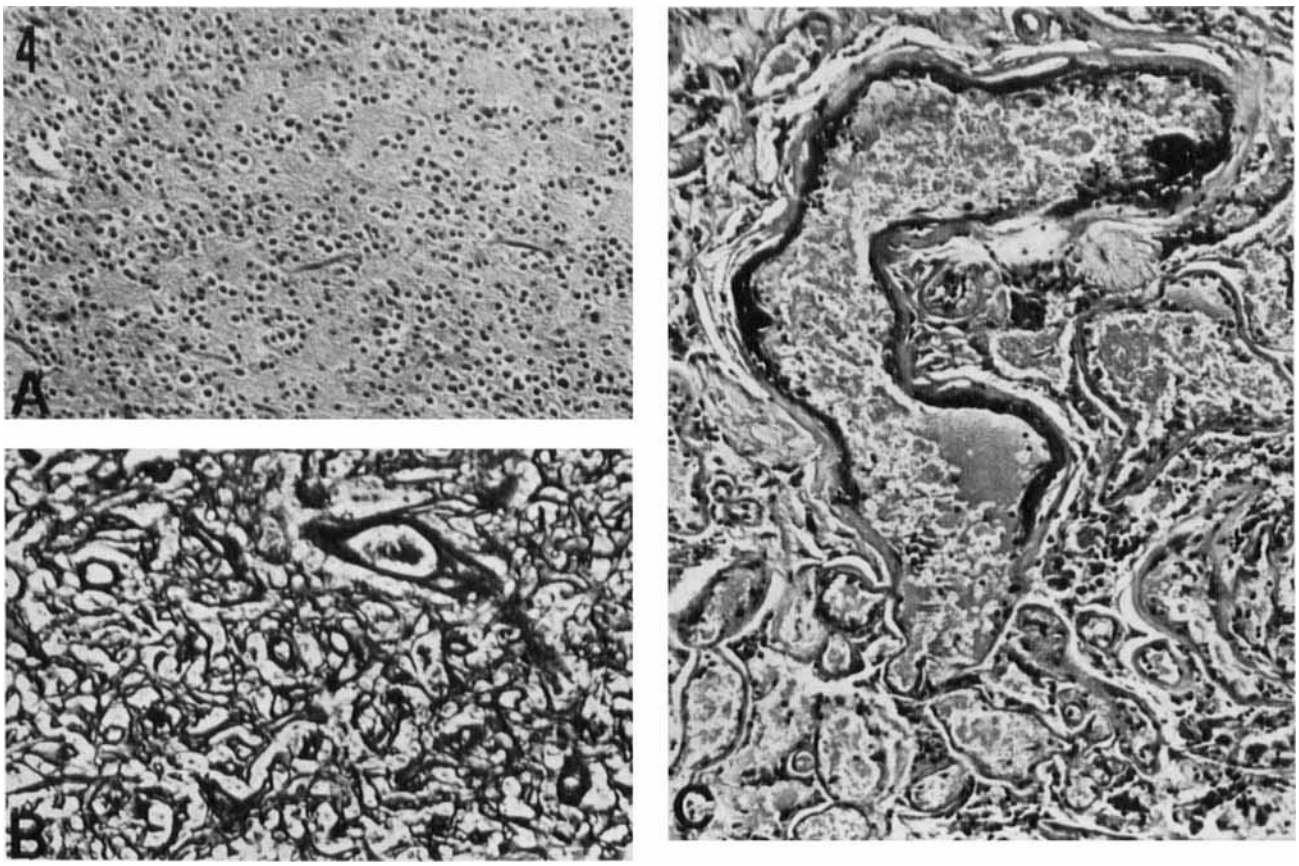

Fig. 4. Microscopic features in Case 5. **A.** Oligodendroglioma with clear cytoplasm of cells (H and E, × 100). **B.** Cluster of blood vessels of various size (reticulin stain × 100). **C.** Some vessels show uneven thickness and calcifical wall (H and E, × 200).

well as in the proliferation of endothelial cell components. Presence of neoplastic neuroglia and excessive number of locally organized and malformed blood vessels could then justify the diagnosis of angioglioma.

Intracranial angioma and glioma may arise either as two separated lesions or may comingle within the same mass. A review of the literature disclosed 41 case reports of solitary intracranial angioglioma including the current study [1,3–5,10,12,19–25], eight cases of two separated tumors either in the same or opposite hemispheres [26–33], and two examples of gliomas that occurred subsequently at the site of the angioma [19,34]. We have not included the two latter conditions in our study, since we are concerned with combined or intermixed tumors within one lesion.

With respect to pathogenesis of angioglioma, at least three mechanisms may be proposed as explanations. First, the proliferated endothelial cells in glioma are potentially neoplastic [1]. This observation is underscored by the demonstration that in experimental gliomas induced by Avian sarcoma virus, the endothelial cells appear to have an extraordinarily high proliferative rate [35]. Furthermore, cases of capillary hemangioblastoma and glioma within the same mass have been described [1,3]. These findings then suggest that these endothelial cells are capable of either being neoplastically transformed or are indeed intrinsically neoplastic.

Second, angiomata may arise initially as a congenital development; then, hyperplastic neuroglia in the region adjacent to the vascular lesion may undergo gliomatous transformation. Several authors have considered the arteriovenous malformation that occurs in the central nervous system to be in reality a maldevelopment [1,16,36]. It is theorized that glioma could arise from areas of reactive gliosis, although such a development is certainly rare [1,28]. Some workers have reported glial neoplasms that have occurred in the site of previously removed or regressed angioma, and even a demyelinating lesion [28,34]. In this case, a cluster of malformed vascular spaces is considered to be a central nidus around which neoplastic glia evolve as depicted in Figure 3 and is partial evidence for this concept.

Third, it is possible that both glioma and angioma could arise independently in different sites within a region eventuating in juxtaposition or resulting in collision of independent neoplasms. Although this concept is difficult to establish histologically, the lesions reported by Heffner et al. and other investigators [26–34] are probably best explained by this mechanism.

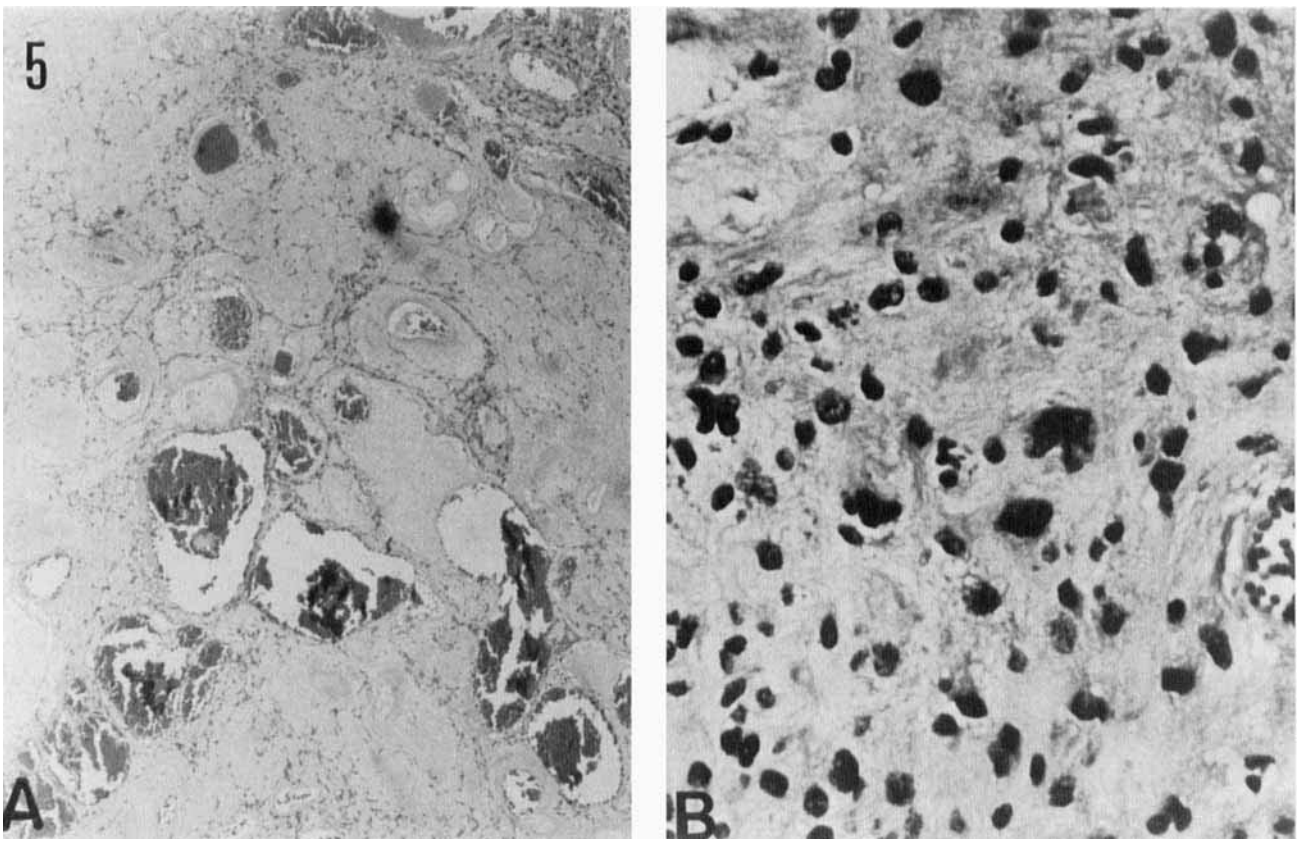

Fig. 5. Photomicrographs in Case 6. **A.** Many hyalinized vessels are noted (H and E, × 40). **B.** Anaplastic astrocytoma showing mitoses and pleomorphism (H and E, × 400).

None of these considerations alone, however, can clarify the occurrence of all such angioglioma. Among 41 cases of angioglioma, there were 19 men, 20 women, and 2 patients for whom gender data was not available. Of these patients, three were in the 1st decade of life, 10 in the 2nd decade, 13 in the 3rd decade, four in the 4th decade, three in the 5th decade, six in the 6th decade, and one in the 7th decade. The youngest patient was a 2-year-old girl; the oldest was a 70-year-old woman [1,20]. The average age was 29.45 years. It should be noted that either intracranial gliomas or hemangiomas occur predominantly in males and often become symptomatic in adults during the 3rd and 4th decades [1,11,36]. Our findings suggest that dual tumors tend to occur in the younger patients, but they may cause symptoms at any age. The reason for the difference in sex from usual gliomas or hemangioma is not known, although in our series, men more commonly have this construct than women. Twelve lesions occurred in the cerebellum, eight in the frontal, five in the temporal, three in the parietal, two each in the temporoparietal, thalamus, posterior fossa, and cerebrum, one each in the occipital, temporooccipital, septum pellucidum, and supratentorium. The tumor thus is most common in the cerebellum, although it may arise in any location of the central nervous system.

What are the effects of the presence of vascular components in a glioma? A partial answer has been offered by Zülch [11], who pointed out that massive hemorrhage may occur in highly vascular gliomata and may result in death. Recurrent attacks of subarachnoid hemorrhage in patients with cerebral angioma accompanying glioma have been reported [26,30]. Xanthochromia cerebrospinal fluid (CSF) was found in a patient with combined arteriovenous malformation and oligodendroglioma [5]. Although the CSF was not examined in our series, all lesions with the set of angioma and glioma have contained foci of hemorrhage and necrosis as well as dense fibrosis. Hemosiderin laden macrophages frequently have been found scattered throughout the lesion, indicating probable previous hemorrhage. Several factors may initiate the bleeding either within the tumor or as a subarachnoid hemorrhage. Hemorrhage may arise from a neoplasm as a result of erosion of vessels, operative manipulation, thrombosis, or necrosis within tumor with loss of vascular support [37]. Rupture of thin-walled or malformed blood vessels may be another important factor as noted in this

series. Liability of these blood vessels to bleeding is increased when one considers the multiple channels of an angiomatous network being present.

With regard to roentgenographic findings in this entity, the arteriograms may detect the vascular component in some cases. For example, among the 11 available case reports with angiograms [3,5,19–22,25], five instances (45%) were described as an arteriovenous malformation [21], arteriovenous fistula [25], and abnormal vasculature [22], as well as vascular mass [3,20]. In our series, four cases (40%) were reported as vascular tumor. Based on these limited data, we suggest that the lesions may be roentgenographic avascular if they contain small calcified vessels, because the minimal patency of the vascular lumen is not sufficient for the contrast materials to accumulate [38]. However, the tumors with large cavernous spaces or arteriovenous component tend to be angiographic detectable.

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